REMARKS

The Office action

Claims 1-5 and 49-51 are pending and under consideration in this application. Claims 6-29 and 40-48 are withdrawn from consideration. Claims 30-39 were previously canceled.

Claims 1-3, 5, and 49-51 stand provisionally rejected for non-statutory obviousness-type double patenting. Claims 1-3 and 5 stand rejected under 35 U.S.C. § 102 for lack of novelty. Claims 1-3, 5, and 49-51 stand rejected under 35 U.S.C. § 103(a) for obviousness. Applicants address each rejection in turn.

Obviousness-type double patenting

Claims 1-3, 5, and 49-51 stand provisionally rejected for non-statutory obviousness-type double patenting over claims 43-45 of copending Application No. 10/948,608; over claim 4 of copending Application No. 11/020,870; and over claim 4 of copending Application No. 11/008,597. Once the pending claims are found to be otherwise allowable except for this ground of rejection, Applicants will address the rejection, including consideration of whether to file terminal disclaimers.

Rejection under 35 U.S.C. § 102

Claims 1-3 and 5 stand rejected under 35 U.S.C. § 102 for lack of novelty over U.S. Patent No. 6,316,433 (hereinafter 'Rose'). As a basis for this rejection, the Office asserts that Rose teaches pharmaceutical compositions in a unit dosage form including rifalazil in amounts of 1 mg and 5 mg. Applicants respectfully disagree and traverse this rejection with the following remarks.

Rose describes rifalazil capsules prepared at four different strengths: 5 mg, 25 mg, 50 mg, and 100 mg (see Rose from column 32, line 64, to column 33, line 5). Furthermore, Rose teaches a dosing regimen of 1-100 mg of rifalazil once or twice weekly. Notably, nowhere in Rose is there any teaching of a unit dosage formulation containing 1 mg of rifalazil as asserted by the Office.

Claims 1-3 and 5 require a unit dosage form containing less than 5 mg of rifalazil

Applicants note that claim 1, and dependent claims 2, 3, and 5 are directed to a unit dosage form of rifalazil in an amount between 0.1 and 5 mg, or a narrower range. Specifically, claims 1-3 and 5 do not encompass a unit dosage form containing 5 mg, or more, of rifalazil. Each of these claims require that the amount of rifalazil contained in the unit dosage form fall **between** an upper and a lower limit, and does not encompass the recited limits themselves (e.g., 'between 0.1 and 5 mg' does not include 0.1 mg or 5 mg). For this reason, claims 1-3, and 5 are not anticipated by Rose's teaching of capsules

containing 5 mg, 25 mg, 50 mg, and 100 mg of rifalazil.

Rose does not teach a unit dosage form containing1 mg of rifalazil

Nowhere in Rose is there any teaching of a unit dosage formulation containing 1 mg of rifalazil as asserted by the Office. Rose teaches a dosing regimen of 1-100 mg of rifalazil once or twice weekly. Importantly, however, Rose also teaches that the drug product can be "administered systemically or parenterally, i.e. orally, intravenously, by aerosol, by suppositories or in any other acceptable pharmaceutical form" (see Rose at column 31, lines 51-53). Nowhere in Rose is it required that the dosing regimen of 1-100 mg of rifalazil once or twice weekly be administered in a unit dosage form (e.g., as a tablet, pill, capsule, or caplet).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. The identical invention must be shown in as complete detail as is contained in the claim. MPEP 2131.

Because Rose does not explicitly teach a unit dosage form containing less than 5 mg of rifalazil, claims 1-3 and 5 are not anticipated by Rose.

In view of the remarks above, Applicants request that the rejection for lack of novelty be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 1-3, 5, and 49-51 stand rejected under 35 U.S.C. § 103(a) for obviousness over Rose in view of Remington Pharmaceutical Sciences, 15th Edition, at page 703 (hereinafter 'Remington'), and/or Lithander et al., Br. J. Ophthalmol. 85:374 (2001) (hereinafter 'Lithander'). As a basis for this rejection, the Office asserts that Rose teaches pharmaceutical compositions comprising a unit dosage form of rifalazil in an amount of 1 mg or 5 mg and finds motivation to utilize a loading dose regimen in Remington and/or Lithander. Applicants respectfully disagree and traverse this rejection with the following remarks.

Rose describes rifalazil capsules prepared at four different strengths: 5 mg, 25 mg, 50 mg, and 100 mg (see Rose from column 32, line 64, to column 33, line 5). Furthermore, Rose teaches a dosing regimen of 1-100 mg of rifalazil administered once or twice weekly. As noted above, nowhere in Rose is there any teaching of a unit dosage formulation containing 1 mg of rifalazil.

Remington and Lithander describe the use of a loading dose regimen. Remington provides a generic description of this approach, while Lithander describes the use of a loading dose regimen of itraconazole for the treatment of a fungal infection. Neither Remington nor Lithander teach or suggest the use of rifalazil for any purpose.

When administered at low doses, rifalazil resides in tissues an unexpectedly long time

Applicants have discovered that, when administered at low doses, rifalazil resides in tissues an unexpectedly long time. As a result, therapeutically useful concentrations of rifalazil can be obtained, and maintained, with the administration of doses of less than 5 mg of rifalazil (see the specification from page 1, line 26, to page 2, line 2, and Table 1 at page 35, Example 2 at pages 35 and 36, and Figures 3-7). This long residency time is reflected in the elimination half-life observed for rifalazil, which has been found to vary with dosing level. In contrast to Rose, which teaches a general trend toward shorter elimination half-lives at lower doses of rifalazil (see Table 1 below), Applicants have found that the elimination half live for a 2.5 mg dose of rifalazil is longer than that observed for a 50 mg dose of rifalazil (139.2 hours vs. 110-116.2 hours).

Advantageously, Applicants discovery of the long tissue residency time observed for rifalazil administered at low doses allows for a therapy in which the amount of rifalazil administered is reduced overall and there is a reduction in the risk of adverse reactions (see the specification from page 1, line 26, to page 2, line 2).

Table 1

Source	Dosing Level	Elimination $t_{1/2}$ Hours
Rose	300 mg	205.6[a]
	100 mg	43.1[a]
	50 mg	110[b]
	30 mg	48.7[a]
	25 mg	61[b]
Applicants	50 mg	116.2[c]
	2.5 mg	139.2[c]

a. See Rose at col. 14, Table 7.
b. See Rose at col. 22, lines 42-44.
c. See Applicants' specification at page 35, Table 1.

Rose teaches away from frequent dosing regimens

Rose teaches a dosing regimen of 1-100 mg of rifalazil administered once or twice weekly. This dosing regimen was arrived at based upon the safety profile observed for rifalazil at various dosing levels and frequencies as noted at column 32, lines 50-63, which recite:

> Dose selection for this study was based on the safety profile of rifalazil obtained from three previous safety and pharmacokinetic (PK) studies. The results of these studies indicated that the incidence of adverse reactions was greater following daily dosing than after a single dose and that the adverse reactions were more prolonged following daily dosing. Furthermore, there appeared to be a dose-dependent trend in the incidence of adverse reactions. A single 300 mg dose did produce more adverse reactions than either the 30 mg or 100 mg single dose. Similarly, approximately twice as many adverse reactions were recorded for the 25 mg daily dose group (003 trial) than for the 5 mg daily dose group and the adverse reactions were more prolonged than following a single dose.

Accordingly, Rose teaches that an increase in dosing frequency increases the number of adverse events and reduces safety. For example, with respect to a regimen of 5 mg per day of rifalazil, Rose at column 18, lines 1-10 recites:

> As seen in Tables 10 and 11, in Group 2 (5 mg/day), all eight subjects receiving drug reported at least one adverse reaction, compared to one of four placebo subjects. By Day 7, five subjects continued to receive rifalazil while three subjects dropped from the study because of adverse reactions. By Day 10, only one subject was still receiving drug. Dosing was suspended after Day 11 by the site investigator. Daily administration of rifalazil was, therefore, found to be unacceptable to the subjects and such daily administration had, to be discontinued.

While Rose also teaches reducing adverse events by reducing dose size, Rose does not describe any specific examples in which the weekly dose is less than 10 mg (see Example 2 at column 33).

In contrast to the compositions taught by Rose, the compositions of the present invention are designed for use as part of a loading dose regimen, which necessarily involves increasing the dosing frequency (see Remington at page 703, figure at the top right column) in comparison to a regular dosing schedule, such as administration once weekly.

The Examiner's use of Remington and/or Lithander to modify Rose is improper

The Examiner's rejection relies upon Remington and/or Lithander to modify Rose to arrive at the compositions of the present invention which are designed for use as part of a loading dose regimen. As Applicants have noted above, Rose teaches away from frequent dosing, such as in a loading dose regimen.

If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. MPEP 2143.01.

Applicants assert that the combination of prior art relied upon for this rejection is improper because the Office is using Remington and/or Lithander to modify Rose in a manner that contradicts the teachings of Rose.

The determination of an optimal dosing regimen is not simple routine experimentation

Finally, the Office states (Office Action at page 5) that "the determination of an optimal dosing regimen is well within the purview of those skilled in the art through no more than routine experimentation." Applicants respectfully disagree and assert that reliance upon this basis for rejecting the claims is improper.

A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references. MPEP 2143.01.

The determination of an optimal dosing regimen is not trivial. As noted above, in the case of rifalazil the determination of the optimal dosing regimen is complicated by the unexpected pharmacokinetic behavior of rifalazil when administered at low doses. This unexpected pharmacokinetic behavior has implications for the design of a safe and efficacious dosing regimen.

In view of the remarks above, Applicants request that the rejection for obviousness be withdrawn.

CONCLUSION

Enclosed is a Petition to extend the period for replying to the Office action for three months, to and including June 21, 2007, and a check in payment of the required extension fee. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Applicants submit that the claims are in condition for allowance and such action is respectfully requested.

Respectfully submitted,

Date: 6/21/07

Michael J. Belliveau, Ph.D.
Reg. No. 52,608

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045